REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-17 and 24-30 are pending in the application subsequent to entry of this Amendment.

Although not discussed in the outstanding Official Action, the claims have been revised to replace "characterized in that" with the more conventional –wherein--. In this process a minor spelling error was corrected (claim 7) and the "preferably", "such as" and "in particular" aspects of claims 5, 7, 8, 11 and 13 have been separated into separate dependent claims. The "use of" claims 18-23 not being of a proper U.S. statutory category have been deleted. Claim 33 is based upon original claim 18. The claims are now believed to be in proper formal order and, for the reasons explained below, directed to patentable subject matter and thus in condition for allowance.

The Official Action raises two prior art-based rejections both based on a single literature reference. Applicants submit that their invention as embodied by the claims now under review is patentable and in no way suggested by the disclosures of the cited prior art.

The Ruch and Matijevic (J. Coil. Interf. Sei 229, 207-211, 2000) article disclose the preparation of budesonide particles -- having a particle size in the micrometer range -- by way of precipitation. This method includes (a) the addition of water as a miscible non-solvent for budesonide to a solution of budesonide in an organic solvent therefor until the budesonide precipitates, a stabilizer being optionally present, or (b) the evaporation of the more volatile solvent component of a mixture of solvent/non-solvent for budenoside at room temperature.

The presently claimed method relates to method of type (a) describe above.

Comparing the particles obtained according to the presently claimed method to those budesonide particles of the cited "Ruch" reference, the present particles are much more stable versus particle size growth than those of Ruch, i.e. the budesonide particles of Ruch are not sufficiently stable and will grow. The dispersions of precipitated budesonide particles show a particle size growth and the dry product cannot be re-dispersed without changes in shape and size. According to Ruch, during the precipitation also ultrasonic treatment is applied for a period of 10 min. The product obtained is separated by filtration through 0.8 μm pores. Thus, the particle size must be above 0.8 μm. The particles obtained are poly-disperse crystals having a particle size distribution of 1 μm to > 10 μm. This is shown by way of SEM

If these methods are carried out with or without the presence of an additive in water such as HPC-SL, no difference in crystal size is observed, only in particle morphology. The essential feature in the Ruch method is the diminution (particle size reduction) of the forming crystallites during the precipitation period by way of ultrasonic treatment. This ultrasonic treatment requires however a certain time (10 minutes).

The other method disclosed [method (b) as mentioned above] uses evaporation of the solvent. As to practical issues, 2 ml budesonide solution are treated with 1 ml 0, 1 wt.-% HPC solution. Upon evaporation budesonide precipitates. Spherical particles result. The particle size depends on the drying rate. If drying is carried out in air larger particles are obtained. If drying is carried out in a vacuum smaller particles are obtained. This is shown by way of the SEM pictures.

Thus, there is only low stabilization against particle growth. Primarily no stable dispersions are produced by Ruch et al because the particles are growing in dispersion. This process of growing can only be stopped by immediate and rapid drying. However, in case of presence of HPC-SL the particles even aggregate as can be seen from the SEM pictures (Fig. 1 and Fig 5). Ruch et al. conclude that HPC-SL cannot prevent aggregation (see page 210, left column), and consequently, the dispersion is not stable. Aggregation can be prevented only when stirring the dispersion. Unfortunately, this results in a change of morphology which might be the result of a process of re-crystallization. This also confirms the insufficient stabilization of the precipitated particles of Ruch et al. If the dispersion is frozen immediately after the precipitation smaller but irregularly shaped particles are obtained. Thus, freezing inhibits diffusion of the particles which would result in particle growth. This effect is widely known. If the dry budesonide particles are re-dispersed in water, their size and shape will be less uniform. This shows the occurrence of changes and confirms that no stable product is obtained.

In contrast to the method of Ruch et al the presently claimed process is conducted in a continuous or discontinuous manner and does not use diminution (particle size reduction) of the precipitated crystallites by way of ultrasonic treatment or any other diminution process such as high pressure homogenization.

The suspension obtained according to the present invention is stable for an extended period of time (12 - 24 h) and during this period of time there is no change in particle size

distribution and no change in habitus as occurs with the Ruch particles.

The process of the present invention does not use evaporation as the Ruch document discloses. After re-dispersion the dried nano- or micro-particles obtained according to the present invention form uniform dispersions. The particles in such dispersions do not change in particle size or shape.

Further, the resulting precipitate does not depend on the process conditions in its properties as the Ruch et al. material does. The present process without depending from the precipitation conditions (continuously or discontinuously, using different mixers or without mixers) results in uniform, stable dispersions.

The present process differs from the Ruch process also in feasibility, because the negative issues described in the Ruch document, such as change in particle shape (morphology), recrystallization and high instability (as the dependency from drying rate shows), do not occur when using the presently claimed process.

The process described by Ruch et al. results in products having sub-optimal properties, while the process of the presently claimed invention results in products having different properties which in turn are optimal for pharmaceutical purposes. These properties are primarily stability of particle size and particle shape in dispersion and the powder formed therewith, which in turn can be re-dispersed to form a stable (without aggregation) dispersion.

As to the above-mentioned improved stability, *see* Figures (e.g. Fig. 1, Fig, 5, Fig. 7, Fig. 9 to 11, Fig. 15) showing that after a considerable period of time there is still the same particle size as precipitated.

Reconsideration and allowance are solicited.

Respectfully submitted,

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